# Impact of DEL22q11, trisomy 21, and other genetic syndromes on surgical outcome of conotruncal heart defects

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**Objective:** Genetic syndromes occur in more than 20% of patients with conotruncal heart defects. We investigated the impact of genetic syndromes on the surgical outcome of conotruncal anomalies in infancy.

**Methods:** This retrospective study reviews the outcome of 787 patients (median age 6.3 months) who underwent primary (598) or staged (189) repair of a conotruncal defect between 1992 and 2007.

**Results:** Proven genetic syndrome was diagnosed in 211 patients (26.8%), including del22q11 (91 patients), trisomy 21 (29 patients), VACTERL (18 patients), and other syndromes (73 patients). Primary repair was accomplished in 80.9% of nonsyndromic patients and 74.4% of syndromic patients ($P = .18$) Fifteen-year cumulative survival was 84.3% ± 2.3% in nonsyndromic patients and 73.2% ± 4.2% in syndromic patients ($P < .001$). Primary and staged repair allowed similar 15-year survival (81.4% ± 4.5% vs 79.1% ± 5.1%, $P = .8$). Freedom from noncardiac cause of death was significantly lower in syndromic patients ($P = .0056$). Fifteen-year Kaplan–Meier survival was 87.6% ± 3.9% for del22q11, 95.8% ± 4.1% for trisomy 21, 56.8% ± 6.3% for VACTERL, and 62.3% ± 12.7% for patients with other syndromes ($P = .022$). Total intensive care unit stay was 10.8 ± 4.9 days in syndromic patients and 5.1 ± 1.7 days in nonsyndromic patients ($P < .001$). Freedom from reintervention 15 years after repair was 79.6% ± 4.9% in nonsyndromic patients and 62.4% ± 7.4% in syndromic patients ($P = .007$).

**Conclusion:** Del22q11 and trisomy 21 do not represent risk factors for mortality after repair of conotruncal anomalies, whereas other syndromes adversely affect the surgical outcome for predominant noncardiac attrition. Higher morbidity and lower mid-term freedom from reintervention can be predicted in syndromic patients.

Supplemental material is available online.

Genetic syndromes occur in more than 20% patients with conotruncal heart defect (CTHD);[1] nevertheless, the impact of this association on the surgical outcome of the cardiac anomalies is still incompletely defined. Previous studies suggested that more than 17% of patients with CTHD carry a 22q11 deletion.[1,2] Moreover, trisomy 21 has been reported in 7% of patients with tetralogy of Fallot (TOF).[3] Patients with TOF with Alagille syndrome carry a mutation in JAG1,[4] and VACTERL, CHARGE, or other syndromes can be associated with TOF[5] and other CTHDs.[6] Patients with CTHD and an associated genetic syndrome present a challenge to the cardiac surgeon and may face additional risk for primary repair. This study was designed to document the impact of genetic defects on the current surgical outcome of CTHD.

## MATERIALS AND METHODS

We reviewed the surgical and medical records of all patients who underwent repair of a CTHD at Bambino Gesù Hospital, Rome, Italy, between January 1992 and January 2007. Informed parental consent and institutional review board approval were obtained for this retrospective study. On the basis of the recommendations of Goldmuntz and colleagues,[1] 6 CTHDs were included in this study because of their possible association with genetic defects, specifically TOF, TOF pulmonary atresia (PA), TOF PA major aortopulmonary collaterals (MAPCAs), truncus arteriosus (TA), double-outlet right ventricle (DORV), and interrupted aortic arch (IAA). Posterior malalignment-type ventricular septal defect (VSD) was not included because it was always found to be associated with IAA in this cohort. Patients with DORV and straddling atrioventricular (AV) valve, hypoplastic AV valve, unbalanced ventricles, or heterotaxy syndromes were excluded because of the rare option of a 2-ventricle repair in these malformation syndromes. Patients with trisomy 13 and 18 also were excluded to avoid the bias of the short and unfavorable natural history in these syndromes. Patients who transferred their care to our unit, but were previously treated at other centers, were excluded from this study. After informed parental consent, a genetic consult by a clinical geneticist (M.C.D.) was obtained to rule out the presence of a genetic syndrome, searching for dysmorphic features, growth anomalies, mental retardation (>6 months of age), and associated malformations. A blood sample was drawn for prospective chromosomal analysis of peripheral lymphocytes using standard and high-resolution techniques. Until 1994, search for microdeletion 22q11.2 relied on Southern hybridization with HD7k probe detecting hemizygosity for the D22S134

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**Abbreviations and Acronyms**

CTHD = conotruncal heart defect
DORV = double-outlet right ventricle
IAA = interrupted aortic arch
MAPCAS = major aortopulmonary collaterals
PA = pulmonary atresia
RV = right ventricle
RVOT = right ventricular outflow tract
TA = truncus arteriosus
TOF = tetralogy of Fallot
VSD = ventricular septal defect

region. After 1994, detection of deletions of chromosomal region 22q11 relied on fluorescent in situ hybridization using the Sc11.1 and N25 probe. Screening was universal for del22q11 and selective for other genetic abnormalities (JAG1, NKX2.5, and others). Fluorescent in situ hybridization analysis with the ENL probe was performed in subjects with clinical characteristics of Williams syndrome. Analysis of medical records with clinical descriptions of associated anomalies, prenatal and postnatal instrumental investigations, and autoptic findings were obtained for the patients who did not undergo genetic testing at birth. Preoperative 2-dimensional and Doppler echocardiography were performed in all patients. Preoperative cardiac catheterization was performed in 187 patients when pulmonary arborization abnormalities such as discontinuous or hypoplastic pulmonary artery branches, multiple aortopulmonary collaterals, presence of multiple VSDs, or anomalous coronary artery patterns were suspected at echocardiography. Cardiac catheterization allowed calculation of total neopulmonary arterial index, pulmonary arterial index, and pulmonary artery-to-collateral arteries lung segment perfusion ratio in the preoperative evaluation of unifocalization and repair of TOF-PA-MAPCAs.[7]

### Operative Technique

Complete repair was accomplished under hypothermic cardiopulmonary bypass (25°C–28°C) for most CTHDs, whereas aortic arch reconstruction in IAA was achieved under deep hypothermic (18°C) circulatory arrest. A systemic-to-pulmonary shunt, if present, was divided. Ventricular septation was accomplished through a transventricular approach in TA, TOF-PA-MAPCAs, and occasionally in DORV, whereas a transatrial approach was preferred in TOF and IAA. VSD closure with 1-stage unifocalization in TOF-PA-MAPCAs was guided by an intraoperative pulmonary flow study. Relief of right ventricular outflow tract (RVOT) obstruction in TOF and DORV was achieved through a combined transatrial-transpulmonary approach. RVOT reconstruction was accomplished after calibration of the pulmonary annulus and PA branches. Preservation of the pulmonary annulus by complete transatrial repair or limited infundibular patch plasty was accomplished when the Z-score for pulmonary annulus diameter was at least –2. Transannular patching was used when the pulmonary annulus Z-score was less than –2. Conduit interposition between the right ventricle (RV) and the pulmonary confluence was used when indicated (PA, truncus). Associated anomalies were corrected simultaneously. RV pressure and PA saturation were measured after discontinuation of cardiopulmonary bypass to detect residual outflow obstruction and left-to-right shunting. Intraoperative transesophageal echocardiography was performed when residual lesions were suspected after repair.

### Follow-up

All surviving patients were followed in the pediatric cardiology outpatient clinic. Clinical examination, 12-lead electrocardiogram, and 2-dimensional echocardiography were performed at regular intervals to estimate tricuspid valve and RV function/pressure and to detect residual lesions, pulmonary artery branch stenosis, or residual aortic arch stenosis. Hemodynamically significant residual lesions were confirmed at cardiac catheterization before surgical or interventional procedures. Closing time for follow-up was June 2007. Mean follow-up was 62.1 ± 23 months (range 6–178 months) and was complete and updated in 765 patients (97.2%).

### Statistical Analysis

Statistical analysis was conducted with the SAS Statview 1998 statistical software (SAS Institute Inc, Cary, NC). Chi-square analysis was used to compare discrete variables between syndromic and nonsyndromic patients, and continuous variables (expressed as mean ± standard deviation) were compared by unpaired *t* testing. Categoric analysis was conducted by chi-square and Fisher's exact tests. Freedom from time-related events was conducted according to actuarial or Kaplan–Meier technique; the resulting curves with 95% confidence limits were compared with log-rank testing, and nomograms of the hazard function were obtained . Selected and separate end points were defined as death, reoperation, or interventional procedure. Early mortality was defined as death within 30 days from surgery or before hospital discharge. Variables associated with an increased risk of death and reoperation were assessed by univariate logistic regression, multiple logistic regression, and Cox proportional risk multivariate analysis. To avoid colinearity among covariates, only mutually exclusive variables were entered in the multivariate analysis. Therefore, all genetic syndromes were compacted under the covariate ''genetic syndrome.''

## RESULTS

Between January 1992 and January 2007, 787 consecutive patients (438 male and 349 female) underwent primary (598) or staged (189) repair for CTHD. Median age at repair was 6.3 months (range 0.1–214 months)

### Anatomy

Surgical anatomy included 540 patients with TOF (68.6%), 58 patients with TOF-PA (7.4%), 63 patients with TOF-PA-MAPCAs (8%), 45 patients with TA (5.7%), 45 patients with DORV (5.7%), and 36 patients with IAA (4.6%). Type A IAA was diagnosed in 9 patients, type B IAA was diagnosed in 26 patients, and type C IAA was diagnosed in 1 patient.

### Genetic Syndromes

A clinical genetic evaluation was obtained in 755 of 787 patients (95.9%), including 667 of 697 survivors (95.6%) and 88 of 90 nonsurvivors (97.7%). Enrollment was refused in 7 patients. Blood was drawn for chromosomal analysis of peripheral lymphocytes using standard and high-resolution techniques in 733 of 787 patients (93.1%). Proven genetic defect was diagnosed in 211 patients (26.8%), including del22q11 (91 patients), trisomy 21 (29 patients), VACTERL (18 patients), and other syndromes (73 patients). Approximately one third of syndromic patients with CTHDs carried a rare genetic defect and were unsuitable for syndrome-specific analysis. This heterogeneous group of patients was therefore arbitrarily defined as ''other syndromes'' to allow for meaningful statistical analysis and included CHARGE (15 patients), Noonan (11 patients), Cantrell's (6 patients), Kabuki (5 patients), Klippel Feil (4 patients), Turner (2

patients), Alagille (4 patients), Opitz (3 patients), Williams (3 patients), Torell (1 patient), Goldenhar (3 patients), Sotos (1 patient), Waardenburg (1 patient), Townes-Brocks (1 patient), cystic fibrosis (1 patient), residual branchial arch syndrome (1 patient), del 5 p (1 patient), del 8 p (1 patient), and del 10 p (2 patients). Mosaic trisomy-22 (2 patients), translocation 21/17 (1 patient), chromosome 7 anomalies (1 patient), and duplication 18q (2 patients) with associated dysmorphic features were demonstrated in 6 patients. Contingency table plotting surgical anatomy versus type of genetic syndrome is depicted in Table E1.

### Preoperative Noncardiac Surgical Procedures

Thirty-seven patients (4.7%) underwent extracardiac surgery before CTHD repair. A genetic syndrome was demonstrated in 29 cases (78.4%). Twenty-one patients with esophageal atresia underwent primary esophageal reconstruction (14 patients), combined gastrostomy and cervical esophagostomy-associated tracheoesophageal fistula ligation in 1 patient or isolated gastrostomy in 3 patients. Other noncardiac procedures before cardiac repair included colostomy (10 patients), gastrostomy and tracheostomy (2 patients), ileostomy (2 patients), ventriculoperitoneal shunting (1 patient), and pyloroplasty with liver biopsy (1 patient).

### Cardiac Repair

Complete 2-ventricle repair was achieved in 787 patients. Primary repair of CTHD was accomplished in 598 patients (76%), whereas staged repair was performed in 189 patients (24%). Complete primary neonatal repair was accomplished in 109 patients (13.8%). Staged repair was more common in syndromic CTHD (54/211 = 25.6%) compared with nonsyndromic CTHD (110/577 = 19.1%), although this difference was not statistically significant ($P = .18$), therefore suggesting that presence of a genetic defect per se did not represent an indication for surgical palliation. There was no correlation between surgical strategy of primary or staged repair and presence or absence of extracardiac lesions requiring extracardiac surgery (Fisher's exact test $P$ value = .25). Mean age at repair was 6.8 ± 3.2 months in syndromic patients and 5.9 ± 2.7 months in nonsyndromic patients ($P = .28$). Mean weight at repair was 4.9 ± 1.1 kg in syndromic CTHD and 6.3 ± 2.4 kg in nonsyndromic CTHD ($P < .01$). Intracardiac repair was associated with additional cardiac surgical procedures in 149 patients (24.5%), including central or branch PA plasty (74 patients), unifocalization of MAPCAs (44 patients) closure of additional muscular VSD (11 patients), VSD enlargement (1 patient), ligation of left persistent superior vena cava to the left atrium (9 patients), bidirectional Glenn anastomosis as part of one-and-a-half ventricle repair (3 patients), resection of supramitral fibrous ring (2 patients), correction of partially anomalous pulmonary venous connection (1 patient), aortopulmonary window repair (2 patients), ligation of a systemic-to-pulmonary collateral (1 patient), and resection of subaortic fibromuscular ring (1 patient).

### Mortality

Overall mortality after repair of CTHD was 11.4% (90/787). Hospital mortality was 6.6% (38/576) in nonsyndromic patients and 16.6% in syndromic patients (35/211) (Fisher's exact test $P$ value < .001). Seventeen additional late deaths occurred at follow-up in 8 syndromic and 9 nonsyndromic patients. Fifteen-year Kaplan–Meier survival was 84.3% ± 2.3% in nonsyndromic patients and 73.2% ± 4.2% in syndromic patients ($P < .001$) (Figure 1). Primary and staged repair allowed similar 15-year survival in this cohort (81.4 ± 4.5 vs 79.1 ± 5.1, $P = .8$). Table 1 depicts overall mortality according to baseline cardiac anatomy and type of genetic syndrome, therefore showing the control for complexity. A significant difference in survival between syndromic and nonsyndromic patients was demonstrated after repair of TOF, TOF/PA, TOF/PA/MAPCAs, IAA, and TA. Causes of death in syndromic and nonsyndromic patients are depicted in Table E2 and classified in cardiac and noncardiac mortality. Table 2 clearly indicates that 5-year freedom from noncardiac cause of death was significantly lower in syndromic patients. When the potential risk factors for death, identified by univariate analysis (Table E3), were entered in a Cox proportional hazard model, presence of a genetic syndrome and non-TOF diagnosis were identified as independent predictors of mortality (Table E4). Kaplan–Meier 15-year survival was again 79.8% ± 5.6% in nonsyndromic patients without TOF compared with 61.8% ± 7.4% in syndromic patients without TOF ($P = .027$) (Figure 2). A secondary analysis was conducted on the group of 211 syndromic patients to verify the impact of various genetic syndromes on surgical outcome. Fifteen-year Kaplan–Meier survival was 95.8% ± 4.1% for trisomy 21, 87.6% ± 3.9% for del22q11, 56.8% ± 6.3% for

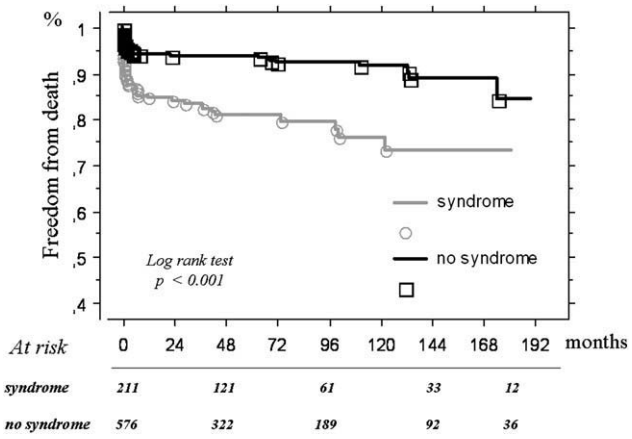


**FIGURE 1.** Kaplan–Meier survival plot in syndromic and nonsyndromic patients after repair of CTHD.

**TABLE 1. Comparison of 1- and 5-year survival in syndromic and nonsyndromic patients stratified by cardiac anatomy**

| | Survival | Syndrome | No syndrome | Log-rank *P* value |
|---|---|---|---|---|
| TOF | 1 y | 90.8% ± 2.8% | 97.1% ± 1.4% | .0026 |
| | 5 y | 88.9% ± 3.1% | 96.9% ± 1.7% | .0012 |
| TOF-PA | 1 y | 86.9% ± 5.7% | 94.1% ± 4.6% | .035 |
| | 5 y | 81.8% ± 6.2% | 93.1% ± 5.4% | .004 |
| TOF-PA-MAPCAs | 1 y | 86.7% ± 4.1% | 91.5% ± 2.7% | .039 |
| | 5 y | 74.2% ± 7.7% | 85.4% ± 5.3% | .033 |
| Truncus | 1 y | 85.3% ± 4.1% | 93.7% ± 3.3% | .006 |
| | 5 y | 81.7% ± 6.2% | 91.3% ± 3.9% | .018 |
| DORV | 1 y | 91.5% ± 4.9% | 96.7% ± 3.1% | NS |
| | 5 y | 88.8% ± 5.9% | 94.8% ± 4.1% | NS |
| IAA | 1 y | 91.9% ± 4.9% | 78.4% ± 5.4% | .031 |
| | 5 y | 86.7% ± 6.1% | 69.8% ± 8.7% | .028 |
| Totals | 1 y | 87.7% ± 2.4% | 94.1% ± 1.1% | .0013 |
| | 5 y | 84.8% ± 2.7% | 93.7% ± 1.3% | .0007 |

*NS,* Not significant. Survival with 95% confidence limits were compared by log-rank testing.

VACTERL, and 62.3% ± 12.7% for other syndromes ($P$ = .022) (Figure 3). Table E5 depicts the analytic description of syndrome-specific outcome with 5-year survival for the subgroup ''other syndromes.'' Table E5 shows that CHARGE, Noonan, Alagille, and Cantrell syndromes were associated with suboptimal 5-year survival. Primary and staged repair allowed similar 15-year survival in the syndromic subgroup (74.3% ± 5.1% vs 71.9% ± 12.8%, respectively, $P$ = .17). Logistic regression confirmed that del22q11 and trisomy 21 were inverse risk factors for death, whereas VACTREL syndrome was a significant predictor of mortality in the syndromic subgroup (Table E3).

## Complications and Reinterventions

Contingency analysis demonstrated significantly higher postoperative morbidity after CTHD repair in syndromic patients (chi-square $P$ value = .039), which accounted for a longer intensive care unit stay compared with nonsyndromic patients (10.8 ± 4.9 days vs 5.1 ± 1.7 days, respectively, $P$ < .001). Further reoperations (131 patients) or alternative catheter procedures with stent or device placement (37 patients) were required in 168 patients (21.3%) to address residual lesions as recurrent VSD (19 patients), residual RVOT or branch PA stenosis (34 patients), combined RVOT obstruction and recurrent VSD (9 patients), or replacement of RV-to-PA conduit (8 patients). Additional procedures included modified-Konno operation for tunnel subaortic stenosis (3 patients), Ross-Konno operation (2 patients), aortic root replacement (1 patient), mitral valve plasty (1 patient), tricuspid valve plasty (1 patient), tracheal patch plasty (1 patient), renal transplantation (1 patient), and combined heart and renal transplantation (1 patient). Alternative catheter intervention included placement of permanent pacemaker for aortic valve block (11 patient) or sinus node dysfunction (1 patient), collateral embolization (8 patients), VSD closure with device (2 patients), or stent placement for branch PA stenosis (17 patients). Freedom from

**TABLE 2. Five-year freedom from death in syndromic and nonsyndromic patients, stratified by cardiac and noncardiac cause of death**

| | Syndrome | No syndrome | Log-rank *P* value |
|---|---|---|---|
| 5-y freedom from noncardiac mortality | 88.7% ± 2.3% | 97.5% ± 0.6% | .0056 |
| 5-y freedom from cardiac mortality | 92.5% ± 2.1% | 95.1% ± 1.6% | NS |
| 5-y freedom from death, any cause | 84.8% ± 2.7% | 93.7% ± 1.3% | .0007 |

*NS,* Not significant. Survival with 95% confidence limits were compared by log-rank testing. Freedom from noncardiac cause of death was significantly lower in syndromic patients.

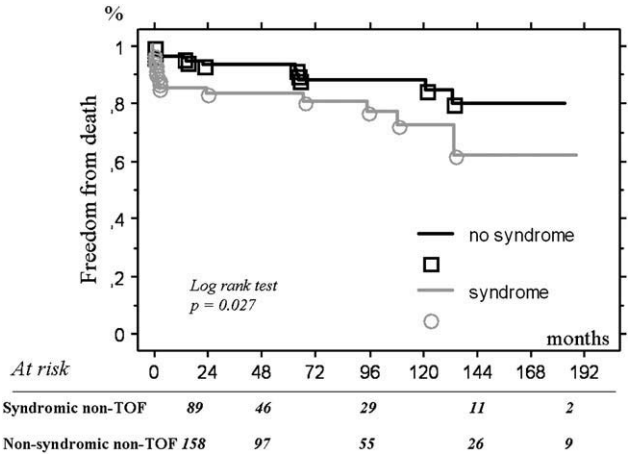


**FIGURE 2.** Kaplan–Meier survival plot in syndromic and nonsyndromic patients with non-TOF CTHD. *TOF,* Tetralogy of Fallot.

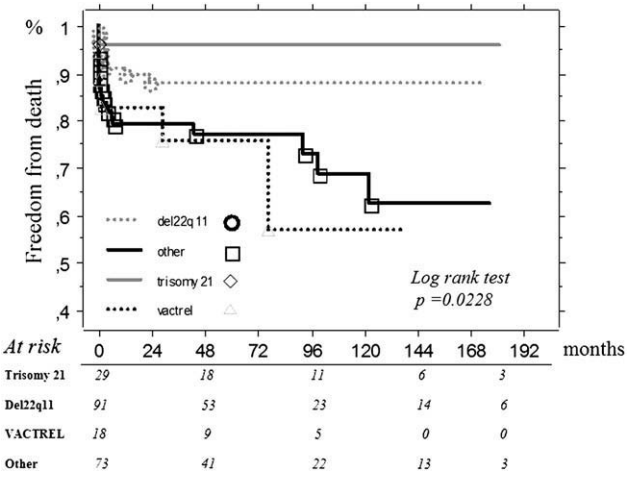


**FIGURE 3.** Kaplan–Meier survival plot in syndromic patients stratified by type of genetic syndrome.

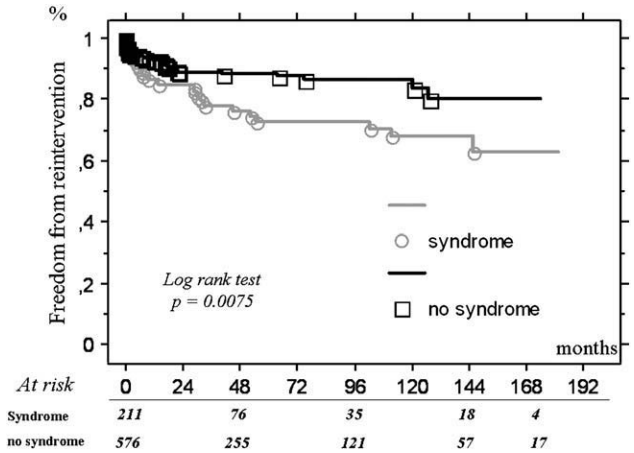


**FIGURE 4.** Kaplan–Meier freedom from reoperation after complete repair of CTHD in syndromic and nonsyndromic patients.

reoperation 15 years after complete repair of CTHD, stratified by presence or absence of genetic syndrome, was 79.6% ± 4.9% in nonsyndromic patients and 62.4 ± 7.4% in syndromic patients ($P = .007$) (Figure 4).

## DISCUSSION

Several genetic abnormalities are currently known to be associated with CTHDs. Previous studies suggested that a substantial number of patients with CTHD carry a 22q11 deletion. Goldmuntz and colleagues[1] reported an incidence of del22q11 in 50% of IAA cases, 34.5% of TA cases, and 15.9% of TOF cases. Approximately 40% of patients with TOF-PA-MAPCAs carry a 22q11 deletion.[7,8] Non-Di George syndromes have been reported to occur in CTHDs, including VACTERL, Alagille, Fryns, and Down syndrome.[9,10] On the other hand, punctiform mutations, such as transcription factor NKX2.5 mutations or ZFPM2/FOG2 gene mutations, have been identified in nonsyndromic TOF.[11,12] The growing identification of genetic causes for well-known genetic syndromes and congenital heart defects such as CTHD prompts the risk assessment of specific genetic defects on surgical outcome of CTHD. This retrospective review demonstrates the impact of various genetic syndromes on surgical outcome of CTHD in recent years. In our cohort of 787 patients, a genetic syndrome was documented in 26.8%. Our analysis shows the following:

1. Fifteen-year survival was 84.3% ± 2.3% in nonsyndromic CTHD and 73.2% ± 4.2% in syndromic CTHD ($P < .001$). Freedom from noncardiac attrition was lower in syndromic patients, mainly because of infective complications. These findings entail the application of specific protocols for antibiotic prophylaxis in syndromic patients undergoing repair of CTHDs. Cox proportional hazard multivariate analysis identified the presence of a genetic syndrome and non-TOF diagnosis as independent predictors of mortality. We previously reported a lower 10-year survival in syndromic patients with TOF compared with nonsyndromic TOF.[13] In this cohort, 15-year survival was significantly worse in syndromic patients without TOF compared with nonsyndromic patients without TOF, and this finding was confirmed for the following anatomic subtypes: TOF/PA, TOF/PA/MAPCAs, and TA. Protract ventilatory support, prolonged intensive care unit stay, and associated extracardiac lesions can explain the worse outcome in syndromic patients with CTHDs in our cohort. These data are in agreement with the experience of Oostehof and colleagues,[14] who identified the presence of noncardiac anomalies as an independent risk factor for death after IAA repair.
2. The novel finding of this analysis is that del22q11 and trisomy 21 were not identified as risk factors for death after repair of CTHDs. Long-term survival in del22q11 and trisomy 21 was comparable with long-term outcome in nonsyndromic CTHDs. These data are in agreement with the experience of Rajasinghe and colleagues[15] and Williams and colleagues,[16] who did not identify Di George syndrome as a risk factor for mortality after repair of persistent TA. Seifert and colleagues[17] recently reported that Down syndrome and elective admission were associated with lower odds of mortality, when evaluating the risk of death in more than 10,200 hospitalizations for pediatric cardiac surgery within the Healthcare Cost and Utilization Project Kids' inpatient database for the year 2000 in the United States. On the contrary, VACTERL syndrome was associated with higher odds of mortality in our cohort, mainly because of infective complications. CHARGE, Noonan, Alagille, and Cantrell syndrome were associated with suboptimal 5-year survival.
3. Freedom from reintervention in syndromic CTHD was significantly lower compared with nonsyndromic patients. Residual RVOT obstruction was the dominant indication for reintervention or interventional procedures in the syndromic subgroup. Central PA hypoplasia and more frequent use of palliative procedures in syndromic CTHD can account for a higher incidence of recurrent RVOTO or branch PA stenosis after cardiac repair.
4. Primary and staged repair of CTHD allowed similar 15-year survival. This finding is interesting because the cohort includes patients who achieved a 2-ventricle repair, therefore excluding interstage attrition. Because there was no significant difference in surgical strategy based on genotype, we speculate that primary cardiac repair could be accomplished even in syndromic patients, whenever a favorable anatomic cardiac phenotype is documented. We suggest that anatomy, not genetics,

should guide a surgical strategy of primary or staged CTHD repair, despite the absolute higher mortality and morbidity observed in syndromic patients.

### Study Limitations

This retrospective study has several limitations. In the absence of a randomized study, it could be argued that palliative procedures were selected for higher risk patients, such as syndromic patients with extracardiac comorbidities or less favorable anatomic patterns, introducing a selection bias in the analysis. Moreover, patterns of surgical treatment of CTHDs might be different at other institutions. This study does not exclude the impact of other anatomic predictors of early mortality that could not be evaluated because of the size of this cohort (ie, truncus IAA). The surgical technique was clearly tailored to the individual anatomy; however, patients with less favorable outcome, such as those with trisomy 13 or 18, were excluded from this study. The cohort included patients who achieved 2-ventricle repair, neutralizing the impact of palliative procedures on surgical mortality. No statistical difference was documented when comparing surgical strategy in syndromic versus nonsyndromic CTHD. There was no correlation between surgical strategy of primary or staged cardiac repair and presence or absence of extracardiac lesions requiring extracardiac surgery. In other words, there was not a selective bias for palliative procedures in higher risk patients with genetic syndrome or extracardiac comorbidities.

## CONCLUSIONS

del22q11 and trisomy 21 do not represent risk factors for mortality after repair of conotruncal anomalies, whereas other syndromes, particularly VACTERL syndrome, adversely affect the surgical outcome for predominant noncardiac attrition. Higher morbidity and lower mid-term freedom from reintervention can be predicted in syndromic patients with CTHDs.

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**TABLE E1. Contingency table plotting type of genetic syndrome versus cardiac anatomy**

| | | Syndrome | | | | |
|---|---|---|---|---|---|---|
| | No syndrome | del22q11 (%) | Trisomy 21 (%) | VACTERL (%) | Other (%) | Totals (%) |
| TOF | 418 (77.4) | 36 (6.7) | 26 (4.8) | 16 (2.9) | 44 (8.2) | 540 (100) |
| TOF-PA | 44 (75.9) | 5 (8.6) | 1 (1.7) | 0 | 8 (13.8) | 58 (100) |
| TOF-PA-MAPCAs | 39 (61.9) | 21 (33.4) | 0 | 0 | 3 (4.7) | 63 (100) |
| Truncus | 29 (64.4) | 11 (24.5) | 0 | 0 | 5 (11.1) | 45 (100) |
| DORV | 30 (66.7) | 3 (6.7) | 1 (2.2) | 0 | 11 (24.4) | 45 (100) |
| IAA | 16 (44.4) | 15 (41.7) | 1 (2.7) | 2 (5.6) | 2 (5.6) | 36 (100) |
| Totals | 576 (73.1) | 91 (11.6) | 29 (3.7) | 18 (2.3) | 73 (9.3) | 787 (100) |

**TABLE E2. Causes of death in syndromic and nonsyndromic patients**

| | Syndrome | No syndrome |
|---|---|---|
| Cardiac | | |
| Low cardiac output | 8 | 18 |
| Diastolic RV dysfunction | 8 | 7 |
| Residual hemodynamic defect | 7 | 7 |
| Pulmonary vascular disease | 1 | |
| Pulmonary vein lesion | | 1 |
| Lobar PA branch lesion (catheter laboratory) | | 1 |
| Pulmonary reperfusion injury | | 1 |
| Arrhythmia | 2 | 4 |
| Noncardiac | | |
| Sepsis | 7 | 4 |
| Mediastinitis | 2 | 1 |
| Enterocolitis | | 1 |
| Respiratory failure | 1 | |
| Hepatic failure | 1 | |
| Airway bleeding | 3 | |
| Cerebral event | 2 | 3 |

**TABLE E3. Univariate logistic regression model coefficient table for mortality**

| | Coefficient | Chi-square | R | *P* value | OR |
|---|---|---|---|---|---|
| Age (mo) | –0.008 | 0.027 | 0.0 | .96 | 0.99 |
| Weight | –0.28 | 0.06 | 0.0 | .8 | 1.0 |
| Sex: male | –0.024 | 0.01 | 0.0 | .9 | 0.97 |
| Genetic syndrome | 1.36 | 24.2 | 0.2 | <.0001 | 3.91 |
| Del22q11 | –1.1 | 16.8 | –0.18 | .008 | 0.21 |
| Trisomy 21 | –1.4 | 26.5 | –0.23 | <.001 | 0.16 |
| VACTERL | 1.22 | 17.53 | 0.24 | .013 | 2.81 |
| Non-TOF diagnosis | 1.43 | 39.8 | 0.26 | <.0001 | 4.18 |
| Extracardiac surgery | 1.09 | 13.4 | 0.14 | .0002 | 2.99 |
| PA hypoplasia | 1.18 | 12.5 | 0.16 | <.001 | 3.2 |
| Anomalous systemic venous connection | 0.49 | 5.6 | .08 | 0.04 | 1.48 |
| Discontinuous PAs | 1.02 | 11 | 0.12 | .022 | 2.89 |
| Multiple VSDs | 0.61 | 2.07 | 0.07 | .15 | 1.4 |
| Anomalous coronary pattern | 0.21 | 1.8 | 0.04 | .66 | 1.25 |
| Conal septal hypoplasia | 0.71 | 2.7 | 0.08 | .045 | 1.8 |
| Staged repair | 0.44 | 1.9 | 0.06 | 0.18 | 1.35 |
| Associated cardiac procedure | 0.84 | 12.7 | 0.13 | .004 | 2.3 |

*R*, Partial correlation coefficient; *OR*, odds ratio.

**TABLE E4. Cox proportional hazard multivariate analysis for mortality**

| | Coefficient | Chi-square | *P* value | OR |
|---|---|---|---|---|
| Genetic syndrome | 0.76 | 9.9 | .016 | 2.14 |
| Non-TOF diagnosis | 1.067 | 18.3 | <.001 | 2.9 |
| Global null hypothesis tests for mortality. Proportional hazard model | | | | |
| Likelihood ratio test | | 28.1 | <.001 | |

*OR*, Odds ratio.

**TABLE E5. Depiction of patients with "other syndromes" stratified by anatomic subtypes**

| | TOF | TOF-PA | TOF-PA-MAPCAs | DORV | TA | IAA | 5-y survival |
|---|---|---|---|---|---|---|---|
| CHARGE | 7 | 4 | 0 | 3 | 1 | 0 | 58.3% ± 16.1% |
| Noonan | 7 | 0 | 0 | 2 | 2 | 0 | 62.5% ± 21.3% |
| Alagille | 4 | 0 | 0 | 0 | 0 | 0 | 54.7% ± 18.4% |
| Cantrell | 2 | 0 | 2 | 2 | 0 | 0 | 23.3% ± 21.2% |
| Kabuki | 2 | 0 | 0 | 3 | 0 | 0 | 100% |
| Klippel Feil | 2 | 2 | 0 | 0 | 0 | 0 | 81% ± 11.5% |
| Turner | 1 | 0 | 0 | 0 | 0 | 1 | 100% |
| Opitz | 3 | 0 | 0 | 0 | 0 | 0 | 80% ± 14% |
| Williams | 2 | 0 | 0 | 0 | 0 | 1 | 71% ± 14% |
| Torell | 1 | 0 | 0 | 0 | 0 | 0 | 100% |
| Goldenhar | 2 | 1 | 0 | 0 | 0 | 0 | 80% ± 15% |
| Sotos | 1 | 0 | 0 | 0 | 0 | 0 | 100% |
| Waardenburg | 1 | 0 | 0 | 0 | 0 | 0 | 100% |
| Townes-Brocks | 0 | 0 | 1 | 0 | 0 | 0 | 100% |
| Cystic fibrosis | 1 | 0 | 0 | 0 | 0 | 0 | 0% |
| Del 5 p syndrome | 1 | 0 | 0 | 0 | 0 | 0 | 100% |
| Del 8 p syndrome | 1 | 0 | 0 | 0 | 0 | 0 | 100% |
| Del 10 p syndrome | 1 | 0 | 0 | 0 | 1 | 0 | 100% |
| Residual br arch | 1 | 0 | 0 | 0 | 0 | 0 | 100% |
| Mosaic trisomy 22 | 1 | 1 | 0 | 0 | 0 | 0 | 100% |
| Translocation 21/17 | 1 | 0 | 0 | 0 | 0 | 0 | 100% |
| Chrom 7 anomalies | 1 | 0 | 0 | 0 | 0 | 0 | 100% |
| Duplication 18q | 1 | 0 | 0 | 1 | 0 | 0 | 100% |
| Trisomy 8 mosaic | 0 | 0 | 0 | 0 | 0 | 1 | 100% |
| Totals | 44 | 8 | 3 | 11 | 5 | 2 | 75.1% ± 11.8% |

Five-year survival is reported.